REMARKS

Claims 151, and 153-160 are pending and under consideration.

Applicants note with appreciation the withdrawal of all of the double-patenting rejections.

In the last Action, the Examiner indicated that claims 152-160 would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims. Although Applicants amended the claims to comport with the Examiner's suggestion, the claims have not been allowed. Applicants respectfully request reconsideration of the claims in view of the amendments and following remarks.

Amendments to the claims

Claim 151 has been amended to add the feature that the first and second promoters of the vector are eukaryotic promoters. Support for the amendment may be found, for example, in the Specification at page 15, line 34 through page 16, line 11. No new matter is added.

35 U.S.C. § 103(a)

The Office Action rejected claims 151, and 153-160 under 35 U.S.C. § 103(a) over U.S. Patent No. 5,561,053 to Crowley ("Crowley") in view of Liu *et al.* (WO 1995/024485, published 09/14/1995) ("Liu"); Mosser *et al.* (1997) *Biotechniques* 22:150-154 ("Mosser"); Bennett *et al.* (1998) *Biotechniques* 24(3):478-482 ("Bennett"); U.S. Patent No. 6,235,967 to Tan *et al.* ("Tan"); and Chishima *et al.* (1997) *Cancer Res.* 57:2042-2047 ("Chishima"). Applicants respectfully traverse.

The invention provides a vector that allows a polynucleotide encoding GFP or an amplifiable selectable marker (*e.g.*, DHFR) to be fused to a polynucleotide encoding a protein of interest to be expressed. Thereby any cell that fluoresces or survives also expresses the protein of interest. Moreover, transfection can be monitored by FACS (from GFP) or by survival all from a dicistronic vector containing 3 proteins: the protein of interest, the amplifiable selectable marker and GFP.

Crowley teaches a *monocistronic* vector in which the polynucleotide encoding the gene of interest is under the control of the same promoter that regulates an amplifiable selectable

marker (*i.e.*, DHFR). Crowley neither teaches nor suggests a dicistronic system or the use of GFP.

Liu does not make up the deficiencies of Crowley as Liu teaches a *tricistronic* vector having three discreet transcriptional units; each with their own promoter and polyadenylation signals. The three separate units express three different gene products. Liu also fails to teach or suggest use of GFP. Moreover, the teachings of Liu and Crowley are fundamentally different from one another and teach away from each other in that Crowley expresses two gene products in a single transcription unit while Liu teaches separation of the gene products into completely separate transcription units. The hypothetical combination of these references undercuts the strategy of each, and is therefore would not be made by one of ordinary skill in the art.

Mosser also does not help in making up the deficiencies of Crowley, even in view of Liu. Mosser teaches a different strategy entirely. Mosser describes on p. 151 that the strategy was to "eliminate the time-consuming process of screening individual clones by transient transfection." Mosser first transfects target cells with a vector that expresses the hygromycin-resistance gene linked to a tetracycline-responsive element and selects the cells using hygromycin. This serves to establish a tTA-expressing cell line in which to introduce further vectors (see Mosser, p. 160, first column, lines 23-27). Subsequently, a hygromycin-resistant population is transfected *with a second vector* which may contain what Mosser describes as a "dicistronic vector" containing a gene of interest and GFP. Notably, Mosser's dicistronic vector uses a single promoter to express *both* the gene of interest and GFP on a single transcript separated by an IRES sequence (see Mosser, p. 156). The presently claimed invention is a dicistronic vector that creates two transcripts, not one, through the use of two promoters. This is a fundamentally different strategy and does not make up the deficiencies of Crowley. First Crowley uses a single transcript system and so does Mosser. The invention creates two transcripts. Second, Mosser's use of the hygromycin-resistance gene was to establish a cell line that contained the tTA-responsive element and not to establish a selection method for the gene of interest as in the invention.

Bennett does nothing to make up for the deficiencies of the above references, even in hypothetical combination as Bennett does not teach or suggest a vector construct as instantly claimed. The fact that one can use GFP in FACS sorting does not in itself or in combination with the above references, amount to a teaching or suggestion a vector system as instantly claimed for which FACS sorting may be employed.

Tan is cited for teaching or suggesting a vector system that includes expression of a protein of interest, an amplifiable selectable marker and GFP. The Office Action frankly admits that Tan fails to teach a system in which the gene of interest is operably linked to either the amplifiable marker or the GFP where the vector comprises both genes regardless. As Tan lacks an essential element of the claims (the presence of all three genes in the claimed association) Tan fails to make up for the deficiencies of Crowley, even in view of the references discussed above. Tan's purpose was to introduce GFP into existing tumor cells to visualize metastasis. There is no express teaching of a vector for expressing GFP, a gene of interest and an amplifiable selectable marker.

Finally, according to the Office Action Chishima teaches a GFP gene mobilized on a vector expressing DHFR and a desired protein (*i.e.*, β-lactamase). However, β-lactamase is a protein that is produced by bacteria and confers resistance to β-lactam antibiotics (*e.g.*, penicillin). Incorporation of β-lactamase in the pED vector is to allow propagation of the vector in bacterial cells. Thus, the promoter used in producing β-lactamase is a prokaryotic promoter, not a eukaryotic promoter as instantly claimed. Moreover, the prokaryotic promoter would not be functional in mammalian cells and thus, β-lactamase would not be expressed at all. Thus, Chishima does not teach a vector system to express a protein of interest with GFP and an amplifiable selectable marker and does nothing to make up for the fundamental deficiencies of the above references.

The above references may be considered in the hypothetical combination suggested by the Office Action unless the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified. If the principle of operation of the prior art invention is modified, then the teachings of the references are not sufficient to render the claims prima facie obvious (*In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (see MPEP 2143.01 (VI)). In the hypothetical combination suggested by the Office Action, the principle of operation of Crowley (expression of two gene products in a single transcription unit) would be modified by combination with Liu which teaches separation of the gene products into completely separate transcription units. Crowley is also improperly combined with Mosser which teaches introduction of hygromycin resistance gene in combination with tTA merely to establish a tTA-responsive cell line and it is by necessity performed using a separate vector from any subsequently introduced vector. Introducing all elements together would alter the principle

of operation of Mosser's teaching that a tTA-responsive cell line must first be established prior to subsequent transfection. Tan does nothing to make up for these deficiencies as it offers no teaching of all three essential elements in the same construct. Bennett is also of no moment as the teaching that GFP can be used in FACS analysis has no bearing on the construct itself which may be used for that purpose.

SUMMARY

Applicants believe that this application is now in condition for allowance and respectfully requests that the outstanding rejections be withdrawn and this case passed to issuance. The Examiner is invited to contact the undersigned at (650) 467-3618 in order to expedite the resolution of any remaining issues.

In the unlikely event that this document is separated from the transmittal letter or if fees are required, applicants petition the Commissioner to authorize charging our **Deposit Account 07-0630** for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Respectfully submitted,

GENENTECH, INC.

Date: January 28, 2010

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